PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
11366PC2-ABS/AKB		
International Application No.	International Filing Date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/AU2003/001333	9 October 2003	9 October 2002
International Patent Classification (IPC) or national classification and IPC		
Int. Cl. [7] A61B 5/0402 .		
Applicant		
QUEENSLAND UNIVERSITY OF TECHNOLOGY et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheet(s).

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [X] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

Date of submission of the demand	Date of completion of the report
8 April 2004	7 January 2005
Name and mailing address of the IPEA/AU	Authorized Officer
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU2003/001333

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **2-5, 8-12, 15-16, 18-19** as originally filed,
pages **6, 7, 7a, 13a, 17, 17a** filed with the demand,
pages **1, 13, 14,** received on **20 December 2004** with the letter of **20 December 2004**

☒ the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages **20, 21, 23** filed with the demand,
pages **22 ,** received on **20 December 2004** with the letter of **20 December 2004**

☒ the drawings, pages **1/7-7/7,** as originally filed,
pages , filed with the demand,
pages , received on with the letter of

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/fig.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	**1-20**	**YES**
	Claims		**NO**
Inventive step (IS)	Claims	**1-20**	**YES**
	Claims		**NO**
Industrial applicability (IA)	Claims	**1-20**	**YES**
	Claims		**NO**

2. Citations and explanations (Rule 70.7)

The following documents identified in the International Search Report have been considered for the purposes of this report:

D1 US 5063937 (EZENWA et al)
D2 WO 1996/001586 (REINING INTERNATIONAL LTD.)
D3 WO 2000/040955 (KAIKU LIMITED)
D4 FR 2748928 (JABOURAIN ARTIN PASCAL)
D5 RU 2112416 (COMPUTING ENGINEERING RESEARCH INSTITUTE)
D6 US 4905705 (KIZAKEVICH et al)
D7 WO 1993/018821 (MEDTRONIC, INC.)
D8 EP 0339471 (LIFECOR, INC. PENNSYLVANIA CORPORATION)

The present application defines a method and apparatus that non-invasively determines cardiac function. Multiple frequencies are applied to "outer" electrodes on a patient, with "inner" electrodes on the patient measuring a voltage signal. The voltage signals are converted to impedance signals for each frequency at a time. Impedance values are specifically determined for a zero frequency, a characteristic frequency and at infinite frequency at a number of time intervals. Cardiac function is determined from this time varying group of impedance values.

Document D1 discloses a multiple frequency bio-impedance measuring system, where tissue impedance may be determined at selectable frequencies (column 4 line 63). The frequency may be zero (column 7 line 64), however the concept of determining tissue impedance at zero, characteristic and infinite frequencies at a number of time intervals is not suggested by D1.

Document D2 recites using an impedance cardiogram to evaluate cardiac output. As in the D1, the concept of determining tissue impedance at zero, characteristic and infinite frequencies at a number of time intervals is not suggested.

Continued on supplemental box...

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
P,X EP 1247487	9 October 2002	3 April 2002	3 April 2001

This document discloses measuring cardiac output using impedance values. EP 1247487 measures base impedance Z_o and a time varying change in impedance 'delta' $Z_{(t)}$. The concept of determining tissue impedance at zero, characteristic and infinite frequencies at a number of time intervals is not suggested by this document.

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of V

D3 provides an apparatus for measuring impedance of body matter at individual frequencies within a range of 1 to 800 kHz. With reference to figure 2, it is evident that impedance is measured at zero and a characteristic frequency. Although measuring impedance at an infinite frequency can be extrapolated from figure 2, a time series groups of measurements is not suggested. D4 recites a cardiac detector that measures impedance in a sweep of frequencies. D5 measures impedance at a number of frequencies using an invasive device. None of these documents suggest the concept of determining tissue impedance at zero, characteristic and infinite frequencies at a number of time intervals.

Document D6 provides a device for non-invasive monitoring of a patients heart condition using tissue impedance. D7 discloses measuring impedance at multiple frequencies to assess the functioning of cardiac tissue. In D8 heart applying electrical pulses from a device worn by the patient automatically treats arrhythmia. None of these documents suggest the concept of determining tissue impedance at zero, characteristic and infinite frequencies at a number of time intervals.

Claims 1 to 20 satisfy Articles 33(2) to 33(4) of the PCT. The claimed invention is novel, possesses an inventive step and has industrial application.

HIGH RESOLUTION BIO-IMPEDANCE DEVICE

TECHNICAL FIELD

The present invention relates to a device for measuring a biological parameter such as extracellular fluid in a person and in particular to a non-invasive bio-impedance device for accurately measuring the cardiac output of a person using impedance measurements at multiple frequencies of stimulation.

BACKGROUND OF THE INVENTION

Cardiovascular disease is the greatest health problem in the developed world, accounting for greater than 40% of all deaths. The economic effects of heart disease and stroke, the principal components of cardiovascular disease, on health care systems grow larger as the population ages. Billions of dollars are spent on the treatment and rehabilitation of cardiac patients.

The electrocardiogram (ECG) measures electrical activity of the heart and therefore provides useful information concerning the sequence and pattern of muscular activity of the heart chambers. The ECG does not evaluate, however, the efficiency of the heart as a pump, i.e., it does not show the amount of blood being pumped through the cardiovascular system.

The cardiac output (CO), a quantitative measure of blood flow, is one of the most useful parameters in assessing cardiac capability and is the volume of blood pumped by each ventricle per minute. CO is determined by multiplying the heart rate (HR) and stroke volume (the volume of blood ejected during each ventricular contraction) and is measured in L/minute.

applied and recorded signals at each frequency.

The distance between the inner pair of electrodes is measured and recorded. The height, weight, age and sex of the patient may also be recorded.

One suitable method of demodulation is to use a fast Fourier transformer (FFT) algorithm to transform time sequence data to the frequency domain. Other digital and analogue demodulation techniques will be known to persons skilled in the field.

Impedance measurements are determined (step 5) from the signals at each frequency by comparing the measured voltage signal to the applied current signal. The FFT algorithm will produce a phase and amplitude for the measured signal compared to the applied signal. The phase and amplitude is used to calculate resistance ($X = z\sin\phi$) and reactance ($R = z\cos\phi$) at each frequency. A suitable calibration of the amplitude is required to obtain the complex impedance z.

The resistance R(f) and reactance X(f) are frequency dependent according to the Cole-Cole relationship:

$$Z = R_\infty + \frac{Ro - R_\infty}{1 + (j\omega\tau)^{(1-\alpha)}}$$

It is known that the impedance at zero frequency Z_0, characteristic frequency Z_c and at infinite frequency Z_{inf} can be determined from a Cole-Cole plot (shown in FIG 3) by fitting the measured resistance and reactance at each frequency to the theoretical locus (step 6). The locus is then extrapolated to obtain Z_0, Z_c and Z_{inf} at the x-axis (step 7). Characteristic

This process (steps 1-7) is repeated until sufficient impedance data has been compiled to record at least one cardiac cycle (step 8). In practice, multiple cardiac cycles are required for accurate analysis.

The final step (step 9) is to determine stroke volume and/or other measures of cardiac function. This can be done using the calculations of equation 3 or equation 4. The acquired data is conveniently displayed in the manner exemplified in FIG 4.

The impedance is plotted 41 in FIG 4 as a function of samples. The sampling rate for FIG 4 is 100 samples per second so the x-axis is equivalent to 2 seconds of data.

To provide a time correlation an ECG 43 is recorded and displayed. It is clear that the traces in FIG 4 cover approximately two cardiac cycles. The middle trace 42 is the time derivative dZ/dt of the impedance trace 41. The dZ/dt data is used to determine stroke volume (SV) and other measures of cardiac function.

An apparatus suitable for working the method of FIG 2 is shown schematically in FIG. 5. A signal generator 51 generates the constant current signal at multiple simultaneous frequencies referred to in step 1. The current is applied to a patient 50 using a pair of outer electrodes 56a and 56b attached to the neck region 50A and thoracic region 50B of patient 50.

A voltage is recorded by signal receiver 52 across a pair of inner electrodes 57a and 57b as referred to in step 2. A digital processor unit 53 performs data manipulation to present the current waveform and the voltage waveform in a suitable form to a signal processing unit 54. The signal

14. The method of claim 1 wherein measures of cardiac function are calculated using the following equation:

$$SV = \frac{\rho L^2 \langle dZ/dt \rangle_{max} VET}{Z_B^2}$$

where: SV = stroke volume

$(dz/dt)_{max}$ = maximum rate of change in measured impedance at the beginning of systolic cycle

VET = left ventricular ejection time.

15. The method of claim 1 wherein measures of cardiac function are calculated using the following equation:

$$SV = \frac{L'^3 \langle dZ/dt \rangle_{max} VET}{Z_B}$$

where: SV = stroke volume

$(dz/dt)_{max}$ = maximum rate of change in measured impedance at the beginning of systolic cycle

VET = left ventricular ejection time

L'= thoracic length estimated from the subject's height and weight using a nomogram

16. The method of claim 1 further including the step of measuring and recording the distance between the inner electrodes.

17. The method of claim 1 further including the step of measuring and recording the height, weight, sex and age of the patient.

18. The method of claim 1 wherein the steps of demodulating and determining an impedance at a time, comprises the steps of: